DECONSTRUCTING RISK ENRICHMENT TO OPTIMIZE PREDICTION OF PSYCHOSIS IN SUBJECTS AT CLINICAL HIGH RISK

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ABSTRACT

Importance

Pre-test risk estimation is routinely used in clinical medicine to inform further diagnostic testing in patients with suspected diseases. The overall characteristics and specific determinants of pre-test probability of psychosis onset in subjects undergoing clinical high risk (CHR) assessment are unknown.

Objectives

To investigate the characteristics and predictors of pre-test probability of psychosis onset in subjects undergoing CHR assessment. To develop and then externally validate a pre-test risk stratification model.

Design

Clinical register-based cohort study.

Setting

Subjects were drawn from electronic, real-world, real-time clinical records relating to routine mental health care of CHR services in South London NHS Trust.

Participants

All non-psychotic subjects referred on suspicion of psychosis risk and assessed by the Outreach and Support in South London (OASIS) CHR service from 2002 to 2015.

Main outcomes and measures

Primary outcome: pre-test probability of psychosis onset in subjects undergoing CHR assessment. Predictors: age, gender, age x gender interaction, ethnicity, socioeconomic status, marital status, referral source and referral year.

Analyses: model development and validation was performed with machine learning methods based on Least Absolute Shrinkage and Selection Operator (LASSO) for Cox proportional hazards model.

Results

A total of 710 non-psychotic subjects undergoing CHR assessment were included. The cumulative six-year pre-test risk of psychosis was 14.55% (95% CI 11.71% to 17.99%), confirming substantial risk enrichment during the recruitment of subjects undergoing CHR assessment. Ethnicity and source of referral were significant predictors of pre-test risk enrichment. The predictive model based on these factors was externally validated showing moderately good discrimination and sufficient calibration. It was used to stratify subjects undergoing CHR assessment into four classes of pre-test risk (six-year): low 3.39% (95%CI 0.96% to 11.56%), moderately low 11.58% (95%CI 8.10% to 16.40%) moderately high 23.69% (95%CI 16.58% to 33.20%) and high 53.65% (95%CI 36.78% to 72.46%).

Conclusions

Significant risk enrichment occurs before subjects are assessed for a CHR state. The ethnicity and source of referral predict pre-test risk enrichment in subjects undergoing CHR assessment. A stratification model can identify subjects at differential pre-test risk of psychosis. Identification of these subgroups may inform outreach campaigns, subsequent testing and optimize psychosis prediction.

INTRODUCTION

The detection of subjects at clinical high risk (CHR) of developing psychosis[1] is increasingly recognized as an important component of clinical services for early psychosis intervention[2] (e.g. NICE guidelines[3], recent NHS England Access and Waiting Time AWT standard[2] and DSM-5 diagnostic manual[4]). Relying solely on the CHR signs and symptoms leads to a correct two-year disease prediction in approximately one third of cases[5]. To improve psychosis prediction, several prognostic models have been applied to stratify the risk levels of subjects who have been assessed on suspicion of psychosis risk and test positive for the CHR criteria[6,7].

However, recent evidence suggests that risk enrichment occurs even before subjects undergo a CHR assessment (pre-test risk) and are assigned to a test outcome (post-test risk, see[8]). Therefore, the degree of risk associated with meeting CHR criteria depends on the variance of pre-test risk enrichment in the subjects being assessed[9] (e.g. lower pre-test risk dilutes the post-test risk[10], see also Table 2 in[9]). The meta-analytical pre-test risk (within 38 months) of psychosis across eleven independent studies conducted worldwide (Europe, North America, Australia, Asia, n=2519) was of 15%, with high heterogeneity (95% CI: 9%–24%)[11] across sites. The meta-analytical clinical gain of testing positive for CHR was relatively modest (as indexed by a small positive likelihood ratio[8] of 1.82[9]) and associated with a 26% risk of developing psychosis (within 38 months)[9], in line with previous estimates[12]. Thus, pre-test risk enrichment in these samples is substantial and heterogeneous[11], accounting for the majority (15/26=58%)[9] of their actual risk. Unfortunately, predictors of pre-test risk enrichment in subjects with suspected CHR are unknown. Meta-analytical evidence suggests that the type of recruitment strategies and outreach

campaigns may affect pre-test probability in subjects undergoing CHR assessment[11]. On the basis of existing knowledge of risk factors associated with psychosis, age[13,14], gender[13], interaction age x gender[13], ethnicity[13], socioeconomic status[15], marital status[16] and referral year[12] may additionally modulate pre-test risk in subjects undergoing CHR assessment. Characterizing and understanding pre-test risk enrichment is necessary to optimize psychosis prediction[10] and improve the clinical practice.

We present here the first original study exploring the characteristics of pre-test probability of psychosis onset in a large sample of subjects undergoing CHR assessment over a long-term follow-up period. We additionally investigated potential predictors of pre-test probability in subjects with a suspected CHR state and suggested a clinical pre-test risk stratification model.

METHODS

Sample

We included all non-psychotic subjects assessed on suspicion of psychosis risk by the Outreach and Support in South London (OASIS) CHR service[17]. All subjects referred to the OASIS in the period January 1, 2002 to December 31, 2015 were initially considered eligible. Then, we discharged those who were referred but never assessed by the team and those who were already psychotic at baseline. The remaining sample was therefore composed of all non-psychotic subjects undergoing a Comprehensive Assessment of At Risk Mental State (CAARMS)-based CHR assessment[18] at the OASIS. Details of the clinical care received at the OASIS team have been described elsewhere[19].

Study measures

Outcome variable

The primary outcome of interest for the current study was the cumulative pre-test risk of developing psychosis in non-psychotic subjects undergoing a CHR assessment. Psychosis onset was defined by the presence of ICD-10[20] diagnoses of psychotic disorders in the electronic clinical records (see below). Time to diagnosis of a psychotic disorder was measured from the date of first referral to OASIS, censored at February 1, 2016.

Predictor variables

The predictors of the pre-test risk in subjects undergoing a CHR assessment were as follows: age[13], gender[13], ethnicity[13] (black, white, Asian, Caribbean, mixed and other), marital status[16] (married, divorced or separated, single and in a relationship), referral year[12] (2002–2005, 2006–2010 and 2011–2015), referral source[11] (self, carers or relatives, schools and colleges, social services or supported accommodations, general medical practitioners, community mental health services, inpatient mental health services, child and adolescent mental health services, early intervention for psychosis services, accident and emergency departments, police and criminal justice system and physical health services), socioeconomic status[15] (index of multiple deprivation, IMD[21]) and the interaction age x gender[13]. All predictor data obtained were those closest to the time of first referral to OASIS. Antipsychotic exposure during follow-up was additionally extracted as confounding factor.

Procedure

This was a clinical register-based cohort study. Outcome and predictor measures were automatically extracted with the use of the Clinical Record Interactive Search (CRIS) tool[22] (see eMethods for details on CRIS).

Statistical analysis

Sociodemographic characteristics of the sample were described with mean and standard deviation for continuous variables and absolute and relative frequencies for categorical variables. To investigate the characteristics of pre-test risk of psychosis onset in subjects undergoing the CHR assessment, we reported its cumulative incidence, estimated by the Kaplan–Meier failure function (1 – survival)[23] and Greenwood 95% CIs[24]. We further used smoothed curves to describe the baseline hazard function[25], computed with kernel density estimation.

Model development and validation followed the guidelines of Royston et al[26] and was performed with a machine learning method that is recommended in the TRIPOD checklist[27], the Least Absolute Shrinkage and Selection Operator (LASSO) for Cox proportional hazards model. LASSO is penalized regression analysis method that performs both variable selection and regularization (shrinking the sum of the absolute values of the regression coefficients[28]) in order to enhance the prediction accuracy and interpretability of the statistical model it produces. LASSO is particularly indicated to control overfitting problems when the number of events is small[29]. We used k-fold cross-validation (repeated 100 times) to find the optimal value of shrinkage parameter λ that gives the minimum mean cross-validated error. Because of significant sociodemographic differences between the borough of Lambeth and the other boroughs (see table 1 and figure 2 and 3 from[30]) we used nonrandom split-sample development and external validation[27], with the Lambeth cases in the

derivation sample and all the other cases in the validation sample. First, the model with all the candidate predictors (categorical predictors were split into dummy variables) was fitted to the derivation data to estimate the optimal regression coefficients. Applying the model selected by LASSO to each case of the derivation dataset, we then generated individual prognostic scores, allowing a four-level (defined with the 25°, 75°, 95°percentiles) prognostic index (PI) for pre-test probability to be developed in the derivation dataset[31]. The regression coefficients estimated in the derivation datasets were then applied to each case in the validation dataset to generate prognostic scores and the PI. Model performance was assessed with the calibration slope (discrimination, model fit)[26], calibration intercept (calibration)[32], Kaplan-Maier curves for risk groups (discrimination, calibration)[26], Harrel's c-index (discrimination)[26] and hazard ratios across risk groups (discrimination)[26]. In a further step we updated the model refitting it to the whole sample rerunning the LASSO, and we tested the confounding effect of antipsychotic exposure. As a supplementary analysis, we additionally reported the risk of psychosis in subjects referred for, but not undergoing, a CHR assessment. All analyses were conducted in STATA 13 (STATA Corp., TX, USA) and R 3.3.0 (package glmnet version 2.0-5).

RESULTS

Sociodemographic and clinical characteristics of the sample

From 2002 to 2015, a total of 1115 subjects were referred to the OASIS clinic for CHR assessment. Among them, 125 subjects did not undergo the CHR assessment and had no contacts with the OASIS service. An additional 280 subjects were already psychotic at baseline (the clinical fate of these subjects is described elsewhere[33]). A final sample of 710 non-psychotic subjects who underwent CHR assessment was used

in the current study (Table 1).

The mean follow-up was of 1472 days (median 1181, range 8-5015). The average age was 23 years, with 56% males. Half of the sample was of white ethnicity. The vast majority was single. Approximately one third of referrals (34%) came from general practitioners. The IMD score was 32% (see eResults 1). Characteristics of the derivation and validation datasets are appended in the eTable 1.

Pre-test risk of psychosis in subjects undergoing CHR assessment

The cumulative incidence (Kaplan–Meier failure function) in the 710 subjects undergoing the CHR assessment is depicted in Figure 1. There were 570 subjects at risk at 1 year, 445 at 2 years, 370 at 3 years, 308 at 4 years, 260 at 5 years. The cumulative pre-test risk of psychosis was 14.55% at six years (95% CI 11.71% to 17.99%). The Kaplan–Meier survival function and the smoothed hazard function are reported in eFigures 1 and 2, respectively. There were 81 events, with the last transition observed at day 2192 (i.e. at 6.01 years)(see eResults 2 for the specific diagnoses), when 193 subjects were still at risk. The mean time to event was 4376 days (i.e. 11.98 years, SE = 67 days, 14^{th} centile = 2099 days).

Predictors of pre-test probability in subjects undergoing CHR assessments

Model development

The LASSO Cox regression analysis in the derivation dataset selected ethnicity and source of referral as predictors of pre-test risk of psychosis onset. The PI showed moderately good discrimination in stratifying four groups at differential pre-test risk of psychosis. Kaplan-Meier curves and discrimination indexes are detailed in eFigure 3 and eTable 2.

Model validation

The PI estimated in the validation dataset retained moderately good discrimination and sufficient calibration (eFigure 4 and eTable 2). The calibration slope was 0.759 and not different from 1 (95%CI 0.346 – 1.173), the calibration intercept was -2.405.

Model updating

The model selected in the development phase, based on ethnicity and source of referral, was then updated in the entire sample. The final coefficients and the equation to estimate the PI are detailed in the eTable 3. The PI defined four classes of risk that were associated with distinctive pre-test probability of psychosis (Figure 2 and Table 2). Harrel's c-index in the updated model was 0.70. For descriptive purposes, we also reported the cumulative incidence for different source of referral at the time of the last failure, 2192 days, in eFigure 5. Ethnicity and source of referrals survived as predictors of pre-test risk when antipsychotic exposure was entered in the model (172 subjects [26%] received antipsychotic treatment during follow-up).

Supplementary analyses are reported in the eFigure 6.

DISCUSSION

This is the first original study to describe the characteristics of pre-test probability of psychosis in a large sample of subjects undergoing CHR assessment and followed up over the long term. The cumulative six-year pre-test risk of psychosis was 15%, confirming risk enrichment during the recruitment of subjects undergoing CHR assessment. Ethnicity and source of referral were significant predictors of pre-test risk

enrichment. A predictive model was externally validated and used to stratify subjects undergoing CHR assessment into four classes of pre-test risk.

The first aim of this study was to address characteristics of the pre-test risk of psychosis in subjects referred to high-risk services and undergoing CHR assessment. In the largest 'real world' sample of subjects undergoing CHR assessment and with the longest follow up published to date, we confirmed a 15% pre-test risk of developing psychosis at six-year follow up (Figure 1). This risk is well in line with previous meta-analytical estimates (which did not include the current data)[9] and it is 35 times higher than the six-year 0.43% risk of psychosis in the local general population (Figure 3). Thus, we confirm the substantial risk enrichment occurring before the CHR assessment. We also report, for the first time, the pre-test baseline hazard function over time (eFigure 2), which indicates a higher risk in the first years following referrals and the last transition observed at six years. Such a time course parallels the actual risk of transition to psychosis reported in CHR samples[5]. Of relevance, in the supplementary analysis, we additionally found that subjects referred to the CHR service but not assessed had a comparable high risk of psychosis (12%) and that this level of risk was still higher than in the local general population. This may support the case for a more assertive approach to the assessment of subjects referred to CHR services[34].

The second aim was to investigate potential predictors of pre-test probability of psychosis onset in subjects undergoing CHR assessment. We found that pre-test risk of psychosis was modulated by ethnicity, with reduced risk in white (HR=0.53, eTable 3) or mixed-ethnicity subjects (HR=0.64, eTable 3) and increased risk in

Asian (HR=1.23, eTable 3) or Caribbean (HR=1.23, eTable 3) subjects. The impact of ethnicity on psychosis incidence has recently been confirmed by meta-analytical studies[13]. There is specific evidence for Asian or Caribbean ethnicity to be associated with a higher risk of developing psychosis than white ethnicity (figure 3 from reference [13]), even after controlling for socioeconomic status[35] (we found no effect for the IMD score). We also found that source of referrals modulate pre-test risk, with reduced risk in self (HR=0.25, eTable 3), carers or relatives (HR=0.27, eTable 3), school or colleges (HR=0.628, eTable 3), social services and supported accommodation (HR=0.27, eTable 3), child and adolescent mental health services (HR=0.62, eTable 3), police and criminal justice system (HR=0.64, eTable 3) referrals and increased risk from inpatients mental health units (HR=7.02, eTable 3), early intervention for psychosis services (HR=2.43, eTable 3), community mental health services (HR=1.36, eTable 3), accident and emergency departments (HR=1.42, eTale 3), physical health services referrals (HR=1.16, eTable 3). These findings confirm that risk enrichment in subjects undergoing CHR assessment is dependent on the adopted recruitment strategies, and therefore, on the referral source[36]. Subjects that had passed through several adult mental health service filters, such as early intervention for psychosis services or inpatient units show the highest risk enrichment (referrals from child and adolescent mental health services show a reduced pre-test risk, in line with studies showing low transition risk in these samples[37]). In contrast referrals outside adult mental health (i.e. self, carer or relatives, schools or colleges, police and criminal justice system, social services) diluted risk enrichment[11]. It is possible to speculate that referrals filtered by adult first episode psychosis or inpatient mental health services may have accumulated risk factors for psychosis (e.g. comorbidities[38]), with more prominent and functionally impairing symptoms so that

transition becomes more likely (for a meta-analysis on functional impairments in CHR subjects see[39]). Variability in referral sources may also explain the high heterogeneity of pre-test risk that has been observed across CHR services wordlwide[41,42]. Overall, our findings inform outreach campaigns, confirming that CHR assessment should be primarily offered to selected samples of subjects "already distressed by mental problems and seeking help for them" (EPA recommendation n.4[14]) and referred from mental health services (in line with the psychometric properties of the CHR instruments[9]), in particular, from early intervention for psychosis services. This brings the CHR paradigm back to its origin. In the first months of operation (1996), the original CHR clinic (the PACE) received the majority of referrals from the local early intervention for psychosis clinic (the EPPIC). As noted by the authors, the early intervention service 'was an important factor' (page 292 from reference[43]) in the recruitment process. Our results also provide scientific support for the new AWT standards in the UK[2], which require CHR assessment to be offered to all subjects accessing early intervention for psychosis services.

Age had no impact on pre-test probability. Meta-analytical evidence indicates that the incidence of psychosis increases from childhood to the age of 20 to 24, then decreases over time (with a age x gender interaction, from figure S4 in reference [13]). It is possible that we did not have enough power to detect significant age effects in the younger subgroup (there were only 30 subjects <16 years in our sample). We also found no effect of referral year on pre-test psychosis risk, suggesting no changes in the patterns of risk enrichment over time. Meta-analyses confirmed no change in the incidence of psychotic disorders over the past decades[13].

In the third aim of this study, we developed and externally validated a prognostic

model to stratify pre-test probability of psychosis onset in subjects undergoing a CHR assessment. The final model was based on simple variables that are easily collected in clinical practice and defined four distinct classes of pre-test risk: low, moderately low, moderately high and high. The high-risk class was also distinct with respect to shorter time to transition. Because the discrimination power of our model was only moderately good[44] (different c-statistics can yield values that are as far as 0.10 apart[45]), sequential testing after initial pre-test risk stratification is required. This may involve an initial CHR assessment to rule out psychosis (on the basis of the large negative likelihood ratio of 0.09 yielded by CHR instruments[9]) and potential additional testing based on more sophisticated neurobiological models. The theoretical potentials of sequential testing in subjects undergoing CHR assessment have been recently illustrated by our group[46]. Pre-test risk estimates and sequential testing have been used since the 1980's[47] in cardiovascular medicine and are still part of the clinical routine to guide and inform further testing and tailored treatments[48], for example in patients with suspected coronary artery disease[49] (e.g. those with chest pain). These patients should receive a thorough history and physical examination to assess the probability of ischemic heart disease 'before additional testing'[50]. Similarly, stratification of low, intermediate and high pre-test probability of recent onset chest pain is currently being recommended by the NICE clinical guidelines (CG95 1.3.3, reproduced in eTable 4). As in the current study, the most widely used parameters are based on simple clinical variables such as the patient's history[51], the description of chest pain, sex and age (table 3 from[47], eTable 4). For the low-risk population, exercise treadmill testing alone is frequently sufficient; however, in patients with a moderate to high risk for coronary artery disease, additional specific testing is usually required[50,52].

Because services and referral patterns are heterogeneous[11] and likely to be influenced by national and local factors, clinical validity of our model should be confirmed and refined by external replication studies conducted in other clinical scenarios. To facilitate this we provided the required statistical information (e.g. eTable 3, eFigure 2) as recommended by international guidelines[26]. Other relevant limitations of this study are related to the use of the clinical case register and are fully discussed in the supplementary material (eLimitations).

CONCLUSIONS

There is substantial risk enrichment during the recruitment of subjects undergoing CHR assessment. Ethnicity and source of referral are predictors of pre-test risk enrichment. A pre-test risk stratification model has been developed and externally validated, which may inform outreach campaigns, help to optimize subsequent testing and the prediction of psychosis.

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Table 1. Sociodemographic characteristics of subjects undergoing CHR assessment at the OASIS clinic (n=710)

	N	Mean	SD
Age (years)(a)	710	23.11	5.37
Index of multiple deprivation (IMD)	710	31.96	8.45
	N	Count	%
Gender	710		
Males		399	56.20
Females		311	43.80
Ethnicity	660		
Black		158	23.94
White		329	49.85
Asian		30	4.55
Caribbean		32	4.85
Mixed		35	5.30
Other		76	11.52
Marital status	627		
Married		19	3.03
Divorced or separated		19	3.03
Single		572	91.23
In a relationship		17	2.71
Referral year	710		
2002-2005		40	5.63
2006-2010		251	35.35
2011-2015		419	59.01
Referral source	710		
Self		66	9.30
Carers or relatives		13	1.83
Schools or colleges		6	0.85
Social services or supported accomodation		11	1.55
General medical practitioners		243	34.23
Community mental health services		165	23.24
Child and adolescent mental health services		61	8.59
Early intervention for psychosis services		47	6.62
Accident and Emergency departments		46	6.48
Inpatient mental health services		14	1.97
Police and criminal justice system		7	0.99
Physical health services		31	4.37
Borough			
Lambeth		321	45.21
Other (c)		389	54.79

(a) age was used as continuous variable, for descriptive purposes only we report here that 30 subjects were under the age of 16 and 680 over the age of 16; (c) Croydon (27), Lewisham (84), Southwark (245) and other areas in Greater London (n=33).

Figure 1. Cumulative incidence (Kaplan-Meier failure function) for the pre-test probability of developing psychosis in subjects undergoing CHR assessment (n=710).

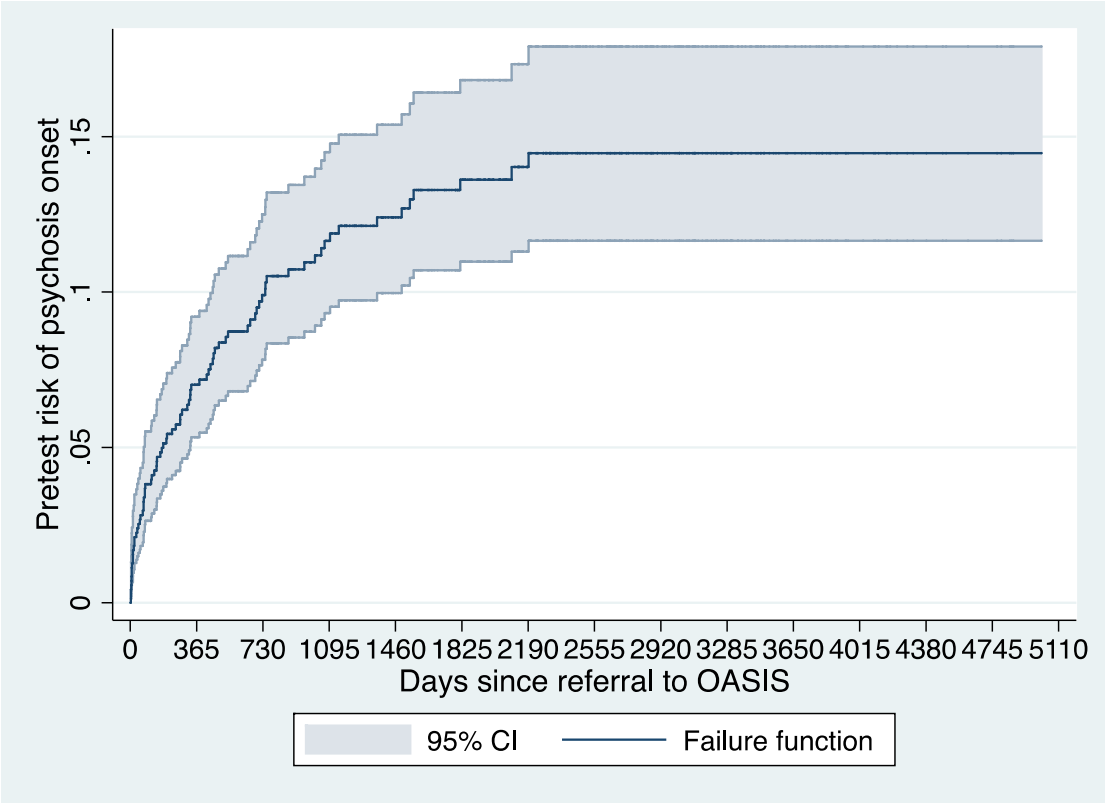

Figure 2. Cumulative incidence (Kaplan-Meier failure function) for risk classes of prognostic index of pre-test probability of psychosis onset in subjects undergoing CHR assessment, model updated in the whole sample.

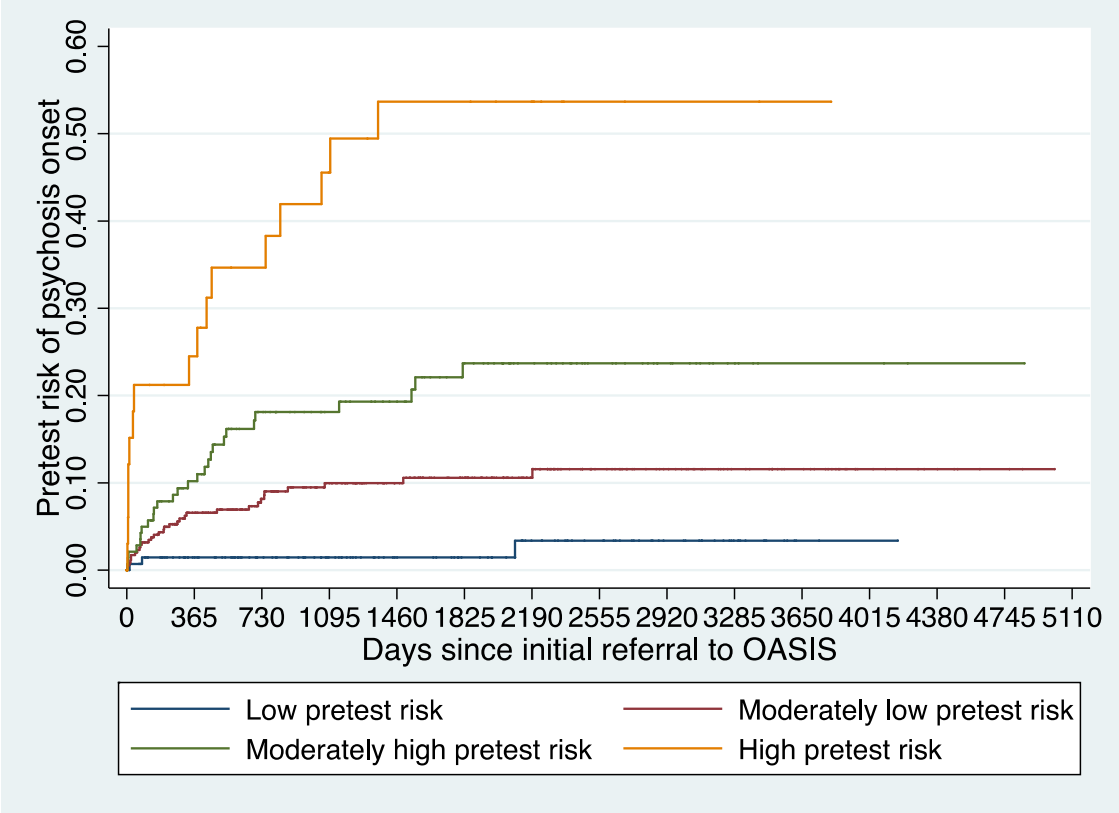

Table 2 Classification of pre-test risk of psychosis in subjects undergoing CHR assessment

	Risk class of the prognostic index			
Characteristics	Low pre-test risk	Moderately low pre-test risk	Moderately high pre-test risk	High pre-test risk
Prognostic score	<-.644	>= -0.644 and <0.203	>= 0.203 and <0.555	>0.555
% of patients	21.06%	52.58%	21.36%	5%
Estimated time to transition, mean (95%CI), days	4067 (3955-4179)	4500 (4328-4672)	3842 (3501-4182)	2017 (1404-2631)
Cumulative incidence, mean (95% CI)				
At month 6	1.45% (0.3% - 5.69%)	4.36% (2.65% - 7.12%)	7.89% (4.45% - 13.79%)	21.21% (10.73% - 39.41%)
At year 1	1.45% (0.3% - 5.69%)	6.58% (4.38% - 9.82%)	10.19% (6.16% - 16.61%)	27.78% (15.51% - 46.66%)
Ay year 2	1.45% (0.3% - 5.69%)	8.16% (5.61% - 11.8%)	18.11% (12.37% - 26.09%)	34.66% (20.83% - 53.94%)
At year 3	1.45% (0.3% - 5.69%)	9.97% (7.02% - 14.04%)	18.11% (12.37% - 26.09%)	45.55% (29.82% - 64.77%)
At year 4	1.45% (0.3% - 5.69%)	9.97% (7.02% - 14.04%)	19.30% (13.28% - 27.57%)	53.65% (36.78% - 72.46%)
At year 5	1.45% (0.3% - 5.69%)	10.58% (7.48% - 14.86%)	23.69% (16.58% - 33.20%)	53.65% (36.78% - 72.46%)
At year 6 (b)	3.39% (0.96% - 11.56%)	11.58% (8.10%-16.40%)	23.69% (16.58% - 33.20%)	53.65% (36.78% - 72.46%)

Moderately low pre-test risk vs low pre-test risk, HR 4.482, SE 2.706; Moderately high pre-test risk vs low pre-test risk HR 9.589, SE 5.836; High pre-test risk vs low pre-test risk HR=27.669, SE= 17.410; Moderately high pre-test risk vs moderately low pre-test risk, HR=2.139, SE= .559; High pre-test risk vs moderately low pre-test risk HR= 6.172 SE=1.890; High pre-test risk vs moderately high pre-test risk HR=2.885, SE= .911; (b) cumulative incidence was censored at the time of the last failure (2192 days), when 193 subjects were still at risk.

Figure 3. Pre-test risk of psychosis in subjects undergoing CHR assessment in South London and in the local age-matched general population. Crude incidence rates for the local population of 16-35 year were estimated with PsyMaptic v.1.0 (http://www.psymaptic.org/) across the borough of Lambeth, Lewisham, Croydon, Southwark.